Exhibit E

Cumulative Effects Associated With Recurrent Concussion in Collegiate Football Players

The NCAA Concussion Study

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Context Approximately 300 000 sport-related concussions occur annually in the United States, and the likelihood of serious sequelae may increase with repeated head injury.

Objective To estimate the incidence of concussion and time to recovery after concussion in collegiate football players.

Design, Setting, and Participants Prospective cohort study of 2905 football players from 25 US colleges were tested at preseason baseline in 1999, 2000, and 2001 on a variety of measures and followed up prospectively to ascertain concussion occurrence. Players injured with a concussion were monitored until their concussion symptoms resolved and were followed up for repeat concussions until completion of their collegiate football career or until the end of the 2001 football season.

Main Outcome Measures Incidence of concussion and repeat concusion; type and duration of symptoms and course of recovery among players who were injured with a concussion during the seasons.

Results During follow-up of 4251 player-seasons, 184 players (6.3%) had a concussion, and 12 (6.5%) of these players had a repeat concussion within the same season. There was an association between reported number of previous concussions and likelihood of incident concussion. Players reporting a history of 3 or more previous concussions were 3.0 (95% confidence interval, 1.6-5.6) times more likely to have an incident concussion than players with no concussion history. Headache was the most commonly reported symptom at the time of injury (85.2%), and mean overall symptom duration was 82 hours. Slowed recovery was associated with a history of multiple previous concussions (30.0% of those with ≥3 previous concussions had symptoms lasting >1 week compared with 14.6% of those with 1 previous concussion). Of the 12 incident within-season repeat concussions, 11 (91.7%) occurred within 10 days of the first injury, and 9 (75.0%) occurred within 7 days of the first injury.

Conclusions Our study suggests that players with a history of previous concussions are more likely to have future concussive injuries than those with no history; 1 in 15 players with a concussion may have additional concussions in the same playing season; and previous concussions may be associated with slower recovery of neurological function.

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THE HIGH INCIDENCE OF CEREbral concussion in contact sports is well documented.[1-8] According to the Centers for Disease Control and Prevention, approximately 300 000 sport-related concussions occur annually in the United States,[9] and the likelihood of serious sequelae may increase with repeated head injury.[10] Recent publications addressing the negative consequences of recurrent concussion in sports raise questions regarding the potential long-term sequelae associated with this injury,[11-13] and recurrent concussion has forced several collegiate and professional athletes to retire early from their respective sports.

Studies from the 1970s report annual concussion incidence rates in high school football to be as high as 15% to 20% of all players in a season,[5,8] while annual incidence estimates of 10% were reported in collegiate football during the late 1980s.[14] More recently, lower in-

See also pp 2556 and 2604 and Patient Page.

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cidence rates of 3.6% and 5.6% have been reported at the high school level.[7,12] Recent studies involving collegiate players have also reported lower injury rates (4.8%[12] and 4.0%[15]) compared with those in the 1980s.

Comparisons between concussion studies are complicated by the lack of universal agreement on the definition of *concussion* and the various levels of severity (ie, grades). An early definition frequently cited is that of a "clinical syndrome characterized by immediate and transient post-traumatic impairment of neural functions, such as alteration of consciousness, disturbance of vision, equilibrium, etc due to biomechanical forces."[16] The hallmarks of concussion are confusion and amnesia, with headache being the most commonly reported symptom. The injury is most often produced by acceleration/deceleration of the freely moving head.[17-19]

Guidelines for return to play following a concussion have been published by several authors[20-25]; however, none has emerged as a criterion standard or been followed with any consistency by sports medicine clinicians. The majority of these guidelines were developed on the premise that athletes may have a reduced threshold for subsequent concussions after an initial concussion. Although this theory has yet to be confirmed in a human model, animal research has identified acute metabolic dysfunction following cerebral concussion that might explain the increased neuronal vulnerability that can exist for several days following injury.[26-30]

The purposes of this study were to examine the association between history of previous concussions and likelihood of experiencing recurrent concussions and to compare time to recovery following concussion between athletes with a history of previous concussion compared with those without a history of previous concussion.

METHODS

We conducted a prospective cohort study of incident and recurrent concussions in a defined group of collegiate athletes. To enroll schools in the study, a letter of inquiry was sent to certified athletic trainers at 36 National Collegiate Athletic Association (NCAA) schools. Certified athletic trainers from 29 schools collected and submitted data, resulting in an initial school response rate of 81%. For the purpose of the final analyses, 4 schools were eliminated because of incomplete data, resulting in an overall school response rate of 69%.

A total of 2905 collegiate football players were enrolled in the study from 19 Division I, 3 Division II, and 3 Division III schools, accumulating 4251 player-seasons of follow-up. Data were collected during 3 football seasons (1999, 2000, and 2001), and players who sustained incident concussions were followed up for repeat concussions until completion of their collegiate football career or until the end of the 2001 season.

Preseason baseline measures were collected at the time of enrollment using a Graded Symptom Checklist (GSC) and an extensive health questionnaire that generated a database of demographic information, concussion history, and preexisting neurological or other medical conditions. *Concussion* was defined as an injury resulting from a blow to the head that caused an alteration in mental status and 1 or more of the following symptoms: headache, nausea, vomiting, dizziness/balance problems, fatigue, difficulty sleeping, drowsiness, sensitivity to light or noise, blurred vision, memory difficulty, and difficulty concentrating.

The GSC was used to quantify the severity of several complaints commonly reported following concussion. Participants rated the presence and severity of 17 symptoms. Each symptom was rated on a 7-point Likert scale ranging from 0 (not present) to 6 (severe). Symptom severity ratings were summed to provide an overall index of symptom severity, as was the total number of symptoms experienced at each postinjury assessment. Although the GSC may be limited by its subjectivity, it has been used in earlier sports concussion studies.[31-34] In addition, we asked the certified athletic trainer evaluating the concussion to complete a series of questions describing the player's course of recovery after concussion. This concussion index served as a record of critical information relevant to injury mechanism, severity, management, duration of symptoms, length of recovery, and return to play.

Procedures

In the event of a concussive injury, the certified athletic trainer administered the GSC at the following assessment points: at the time of injury, 3 hours after injury, and at postinjury days 1, 2, 3, 5, and 7. Athletic trainers completed the concussion index over the course of the player's recovery, tracking the player until he was asymptomatic. Additionally, 17 of the participating schools were randomly assigned to an "assessment group" and were asked to use a brief battery of concussion assessment tools.[35] Members of the research team retrospectively graded concussion severity using the information regarding symptom duration on the concussion index. This study was approved by the institutional review boards for protection of human research subjects at the host institutions of the principal investigators. All participants granted written informed consent prior to enrollment in the study.

Participation in Sport

Collection of detailed data on participation at the level of the individual athlete ("exposure" data) was beyond the resources of this study. We therefore estimated athlete exposures in the playing population based on data from the NCAA Sports Sponsorship and Participation Report[36] and the NCAA Injury Surveillance System.[15] We multiplied the number of athlete-seasons of follow-up in our study by the average number of exposures per athlete (estimated from NCAA data), stratified by division, to produce the estimated athlete exposures for games and contact practices. We did not include noncontact practices in our denominator since these rarely result in concussion.[12]

Statistical Methods

For analyses dealing with the case series of injured players, χ^2 tests of association were used to compare proportions in tables; the Fisher exact test was used when 80% of expected counts were less than 5. To estimate the risk of incident concussion based on playing position and number of previous concussions, we used rate ratios and 95% confidence intervals (CIs) based on standard Poisson assumptions.[37] We controlled for potential confounders using a multivariate generalized Poisson regression model for the rate of concussion.[38-40] This model was implemented using a generalized-estimating-equations approach to account for repeated concussions in the same athlete and clustering of athletes by school.[41,42] Statistical analyses were conducted using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). The level of significance was set a priori at $P<.05$ for χ^2 tests of association.

RESULTS

Descriptive Analysis

The 2905 college football players were followed up for a total of 4251 player-seasons. Our study resulted in 196 reported concussions among 184 players (12 concussions were prospective repeat concussions). Of the 196 incident concussions, 94 were included in the assessment group. The overall rate of incident concussion was 0.81 per 1000 athlete exposures (95% CI, 0.70-0.93). More than half of the total concussions (n=101 [51.5%]) occurred in practices, but the rate of concussive injuries in games was markedly higher than the rate in practices (rate ratio, 8.15; 95% CI, 6.16-10.78). The rate in Division III was also higher than the rates in Divisions I and II (TABLE 1).

When the concussions were retrospectively graded for severity on the Cantu Evidence-Based Grading Scale,[21] most concussions (118/169 [69.8%]) were classified as a grade 2, while only a small percentage were either grade 1 (25/169 [14.8%]) or grade 3 (26/169 [15.4%]) concussions. Insufficient data on symptom duration, memory loss, and loss of consciousness (LOC) for 27 of the concussions prevented us from retrospectively grading all injures. A relatively small segment of players with concussions experienced LOC (12/191 [6.3%]; mean duration, 53 seconds; median duration, 30 seconds) or exhibited signs of amnesia (46/191 [24.1%]; mean duration, 104 minutes; median duration, 30 minutes). Amnesia included anterograde amnesia alone or anterograde amnesia plus retrograde amnesia. There was no LOC or amnesia associated with the majority of concussions (137/191 [71.7%]). Offensive linemen, linebackers, and defensive backs (20.9%, 16.3%, and 16.3% of all players with concussions, respectively) were the most frequent to sustain concussions. The injury rate per 1000 athlete exposures suggests that there is a weak association between position played and likelihood of concussion, since these 3 positions yielded the highest injury rates among the 10 playing positions (TABLE 2). The most common mechanisms by which concussion occurred were collision with an opponent (74/196 [37.8%]), tackling an opponent (42/196 [21.4%]), being tackled by an opponent (33/196 [16.8%]), and blocking an opponent (29/196 [14.8%]).

The most common signs and symptoms reported on the GSC by players

Table 1. Estimated Athlete Exposures and Rate of Incident Concussion per 1000 Athlete Exposures by Level of Competition

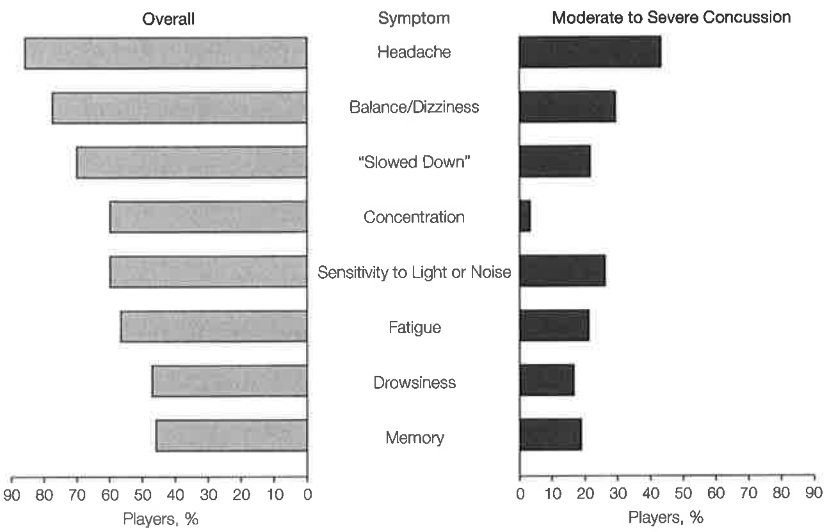
	No. of Incident Concussions	Estimated No. of Athlete Exposures	Concussion Rate per 1000 Athlete Exposures (95% Confidence Interval)
Division I			
Game	68	18354	3.70 (2.82-4.59)
Practice	63	161888	0.39 (0.29-0.49)
Total	**131**	**180242**	0.73 (0.60-0.85)
Division II			
Game	12	3740	3.21 (1.39-5.02)
Practice	14	31693	0.44 (0.21-0.67)
Total	**26**	**35433**	0.73 (0.45-1.02)
Division III			
Game	15	2850	5.26 (2.60-7.93)
Practice	24	22426	1.07 (0.64-1.50)
Total	**39**	**25276**	1.54 (1.06-2.03)
Overall			
Game	95	24944	3.81 (3.04-4.57)
Practice	101	216007	0.47 (0.38-0.56)
Total	**196**	**240951**	0.81 (0.70-0.93)

Table 2. Incident Concussions and Rate per 1000 Athletic Exposures by Player Position

Position	No. of Incident Concussions (% of Overall)	No. of Player-Seasons	Estimated No. of Athlete Exposures	Concussion Rate per 1000 Athlete Exposures (95% Confidence Interval)
Quarterback	11 (5.6)	235	13320	0.83 (0.34-1.31)
Running back	18 (9.2)	447	25336	0.71 (0.38-1.04)
Receiver	15 (7.7)	493	27944	0.54 (0.27-0.81)
Tight end	10 (5.1)	227	12867	0.78 (0.30-1.26)
Offensive lineman	41 (20.9)	760	43078	0.95 (0.66-1.24)
Defensive lineman	28 (14.3)	647	36673	0.76 (0.48-1.05)
Linebacker	32 (16.3)	570	32308	0.99 (0.65-1.33)
Defensive back	32 (16.3)	643	36446	0.88 (0.57-1.18)
Special teams	9 (4.6)	205	11620	0.77 (0.27-1.28)
Total	**196 (100)***	**4227**	**239592**	0.78 (0.67-0.89)

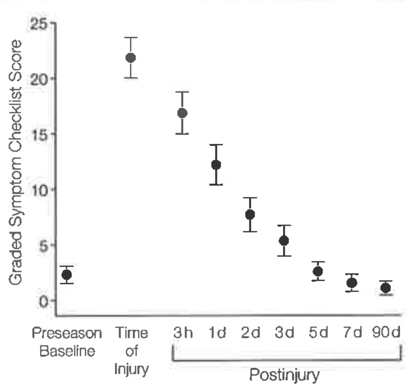
*Percentages do not add to exactly 100% because of rounding.

Figure 1. Percentage of Players With Concussion (n=196) Reporting Symptoms at Time of Injury



Moderate/severe symptoms defined as scores of 3 to 6 on the Graded Symptom Checklist.

Figure 2. Mean Reported Graded Symptom Checklist Total Scores for Players With Concussion (n=196) Across Repeated Assessments



Error bars indicate 95% confidence intervals.

with concussion are presented in FIGURE 1 and mean GSC total scores are shown in FIGURE 2. Headache (167/196 [85.2%]) was the most commonly reported symptom at the time of injury, followed by dizziness/balance difficulties (151/196 [77.0%]) and feeling cognitively "slowed down" (136/196 [69.4%]). Among the 167 players experiencing a headache at the time of their concussion, 149 (89.2%) still reported having a headache 3 hours after injury, 110 (65.9%) 24 hours after injury, 41 (24.5%) at postinjury day 5, and 23 (13.8%) at postinjury day 7. On average, overall symptom duration was about 3.5 days (mean duration, 82 hours; median duration, 48 hours), and 87.8% (172/196) achieved full symptom resolution within 1 week after injury.

There was an apparent association between returning to play on the same day of injury and experiencing delayed onset of symptoms (ie, symptoms not present immediately following the concussion but present 3 hours after injury) (χ^2_1=7.83; P=.005). Thirty-three percent (10/30) of players with concussion who returned to play on the same day of injury experienced delayed onset of symptoms compared with only 12.6% (20/158) of those who did not return to play on the same day of injury. Analysis of headache scores alone found that 9 players (4.6%) with concussion reported a delayed headache, which was not present at the time of injury but was present 3 hours after injury. However, this association could be spurious since players whose symptoms did not resolve within 3 hours were more likely to be withheld from play and who, by definition, did not develop delayed-onset symptoms.

Recurrent Concussion

The likelihood of sustaining an incident concussion was associated with a history of self-reported previous concussion (TABLE 3). Sixty-six (35.1%) of 188 injuries were recorded as "repeat injuries" from within the last 7 years; football players with a history of 3 or more previous concussions were 3 times more likely to sustain an incident concussion than those with no concussion history; and similar elevations in risk, although less marked, were observed in players with 2 previous concussions and those with 1 previous concussion. This "dose-response" relationship between number of previous concussions and risk of incident concussion persisted after controlling for potential confounders, such as division of play, playing position, years of participation in organized football, academic year in school, and body mass index, using multivariate Poisson regression (Table 3). Data collectors reported that 12 (6.5%) of the 184 players with concussion had an incident repeat concussion within the same season. Of the in-season repeat concussions, 11 (91.7%) of 12 occurred within 10 days of the first injury, and 9 (75.0%) of 12 occurred within 7 days of the first injury.

Course of recovery was classified by the certified athletic trainers as either rapid (symptoms lasting <1 day), gradual (symptoms lasting 1-7 days), or prolonged (symptoms lasting >7 days). Athletes with a history of multiple concussions experienced a longer recovery (P=.03 by Fisher exact test) (TABLE 4). There was no association between concussion history (0, 1, 2, or ≥3 concussions) and the presence of either LOC (P=.66 by Fisher exact test) or amnesia (P=.31 by Fisher exact test) with subsequent concussions. However, presence of LOC and amnesia tended to be associated with a slower recovery (TABLE 5). Ten players with concussion (5.4%) were disqualified

Table 3. Association Between Concussion History and Risk of Incident Concussion

No. of Previous Concussions	No. (%) of Incident Concussions*	No. of Player-Seasons	Estimated No. of Athlete Exposures	Concussion Rate (95% CI) per 1000 Athlete Exposures	Rate Ratio (95% CI)	Multivariate-Adjusted Rate Ratio (95% CI)†
0	122 (3.7)	3265	185 060	0.66 (0.54-0.78)	1.0	1.0
1	41 (5.4)	756	42 850	0.96 (0.66-1.25)	1.5 (1.0-2.1)	1.4 (1.0-2.1)
2	15 (10.5)	143	8105	1.85 (0.91-2.79)	2.8 (1.6-4.8)	2.5 (1.5-4.1)
≥3	10 (12.7)	79	4478	2.23 (0.85-3.62)	3.4 (1.8-6.5)	3.0 (1.6-5.6)

Abbreviation: CI, confidence interval.
*Data are expressed as No. (%) of players from each concussion group ($\chi^2_3 = 30.11$; $P<.001$).
†Adjusted for body mass index (by quartile), academic year (freshman, sophomore, junior, or senior/graduate), years of organized football experience (≤7, 8-10, or ≥11), division (I, II, or III), and playing position (listed in Table 2).

from participation for the remainder of the season following their concussive injury, 8 (80%) of whom experienced a prolonged duration of symptoms (mean, 14 days) and 8 (80%) of whom had a history of recurrent injury.

COMMENT

Our results suggest that college football players with a history of concussion are likely to have future concussive injuries. We observed an increase in the likelihood of recurrent injury with each successive previous injury. Given our finding of a 3-fold greater risk of future concussions following 3 concussions vs no concussions, athletes with a high cumulative history should be more informed about the increased risk of repeat concussions when continuing to play contact sports such as football. The multivariate-adjusted rate ratio in our study nearly doubled between the group with 1 previous concussion (rate ratio, 1.4) and the group with 2 previous concussions (rate ratio, 2.5), suggesting that as few as 1 previous concussion may present a cumulative effect. Additionally, we found that 1 in 15 players with concussion may have additional concussions in the same playing season and that these reinjuries typically take place in a short window of time (7-10 days) following the first concussion.

A 1995-1997 study of high school and collegiate football players reported a 14.7% within-season recurrent injury rate.[12] The lower rate of within-season recurrent concussion (6.5%) found in our study can perhaps be explained by increased awareness of the dangers surrounding cerebral concussion in recent years, which is believed to have led to more conservative return-to-play decision making by athletic trainers and team physicians. Fewer players with concussions returned to play on the same day of injury in the current study, which could have attributed to this lower overall injury rate. Further findings suggest that college football players are much more likely to sustain a concussion during a game than during a practice (rate ratio, 8.15). Given that concussions most often result from sudden acceleration/deceleration of the freely moving head,[17-19] this finding can most likely be attributed to the intensity and speed at which the games are played relative to average practice conditions. Linebackers, offensive linemen, and defensive backs may also have an increased risk of concussive injury, which is consistent with previous findings and most often explained by the increased size and speed of players in these positions.[2,12]

Additionally, our study suggests that a history of concussion is associated with prolonged recovery following subsequent concussions (Table 4). The increased risk of future injury, as well as slower recovery, may be indicative of increased neuronal vulnerability following recurrent concussive injuries. Animal studies have described an acute neurometabolic cascade involving accelerated glycolysis and increased lactate production immediately following concussion.[28-30,43-45] The increased lactate is believed to leave neurons more vulnerable to secondary ischemic injury and has been considered a possible predisposition to repeat injury.[26,27] Later steps in this physiologic

Table 4. Length of Symptom Recovery in Players With Concussion by History of Concussion*

Length of Symptom Recovery (d)	No. of Previous Concussions† 0 (n = 122)	1 (n = 41)	2 (n = 15)	≥3 (n = 10)
Rapid (<1)	37 (30.3)	16 (39.0)	5 (33.3)	0
Gradual (1-7)	76 (62.3)	19 (46.3)	7 (46.7)	7 (70.0)
Prolonged (>7)	9 (7.4)	6 (14.6)	3 (20.0)	3 (30.0)

*Data are expressed as No. (%) of players with concussion.
†P = .03 by Fisher exact test.

Table 5. Length of Symptom Recovery in Players With Concussion by Loss of Consciousness and Posttraumatic Amnesia*

Length of Symptom Recovery (d)	Loss of Consciousness†		Amnesia‡	
	Yes	No	Yes	No
Rapid (<1)	1 (9.1)	52 (29.9)	9 (20.9)	44 (30.8)
Gradual (1-7)	7 (63.6)	105 (60.3)	26 (60.5)	87 (60.8)
Prolonged (>7)	3 (27.3)	7 (9.8)	8 (18.6)	12 (8.4)

*Data are expressed as No. (%) of players with concussion.
†P = .09 by Fisher exact test.
‡P = .13 by Fisher exact test.

cascade involve increased intracellular calcium, mitochondrial dysfunction, impaired oxidative metabolism, decreased glycolysis, axonal disconnection, neurotransmitter disturbances, and delayed cell death. Decreased cerebral blood flow has been reported to last approximately 10 days following concussive injuries in animal models,[26] which is consistent with our finding of an apparent 7- to 10-day period of increased susceptibility to recurrent injury. The disrupted cellular metabolism that has been described by researchers as leaving the cells more vulnerable to further injury[26-28,46] should be studied further in human models.

Although previous authors have reported that 85% to 90% of all concussions are mild (grade 1),[2,4,7,22,47] we found a higher incidence of moderate (69%) and severe (15%) concussions in our study based on the most recent Cantu Evidence-Based Grading Scale. This scale classifies more of the concussions as grades 2 and 3 (range, 1-3, with 3 most severe), primarily on the factor of symptom duration. For example, 26 cases were classified as grade 3 because symptoms persisted beyond 7 days after injury, whereas other grading scales classify concussions as severe based solely on the presence of LOC or prolonged amnesia.

According to our findings, concussions manifest with varying signs and symptoms, as well as severity and duration of these symptoms. The signs and symptoms present at the time of injury observed in our study are consistent with those reported by other authors.[2,12,14,20,31,34,47-52] Most concussion grading scales are weighted heavily on the presence of LOC and/or amnesia at the time of injury and for a brief period thereafter. However, previous studies have reported that the majority of concussions involve neither LOC nor amnesia.[7,12,47] Significant debate still exists surrounding the predictive value of LOC and amnesia for recovery and outcome.[21,53] These are only acute markers of injury severity and, as evidenced by our findings, do not clearly predict the duration and intensity of symptoms in players with concussion. Only 6.3% of the observed concussions in our study resulted in LOC, and only 24.1% involved amnesia. We did not find LOC or amnesia to be associated with delayed recovery but did find that an increased number of previous concussions was associated with delayed recovery beyond 1 week after injury. Future studies should prospectively investigate the validity of the various concussion grading scales and clinical management of concussion with respect to outcome.

This study presents information on a relatively large series of concussions in a defined cohort of contact-sport athletes. The data were collected by certified athletic trainers who were present at all football practices and games. However, our data have limitations. It is possible that some players who may have had a concussion during the study period were not identified. Researchers and clinicians have long thought that the rate of concussion is likely underestimated because of the reluctance of some athletes to report or their inability to recognize the signs and symptoms of concussion.[54] Although our study was not exempt from this form of potential selection bias, we attempted to minimize this bias by studying only teams with certified athletic trainers, who were trained in recognizing the signs and symptoms of a concussion and were present at all practices and games.

Furthermore, as described in the "Methods" section, we lacked individual-level data on athlete exposures and had to estimate this information from external sources. This could have some repercussions for our findings. For example, a potential source of bias in our observed association between history of previous concussion and incident concussions is that exposure time (time spent playing football) might differ between those who have a positive history of concussion and those with no history of concussion. To explore this potential bias more fully, we obtained detailed data on total number of games and contact practices for a sample of 120 football players from 2 colleges and found that the mean number of contact exposures tended to be lower in those with a positive concussion history. The mean number of athlete exposures in practices and games for players with 0 previous concussions was 69.3 (95% CI, 66.3-72.3), significantly different from the mean number of athlete exposures for players with 1 previous concussion (59.3; 95% CI, 53.2-65.4) or 2 or more previous concussions (55.3; 95% CI, 39.4-71.3) ($F_{2,117}=7.18$; $P<.001$), suggesting that our data may have understated the strength of this association. The observed trend was consistent across all levels of player status (starter, reserve, and predominately practice player).

CONCLUSION

These results illustrate that a history of previous concussions may be associated with an increased risk of future concussive injuries and that these previous concussions may be associated with slower recovery of neurological function following subsequent concussions. Within a given season, there may be a 7- to 10-day window of increased susceptibility for recurrent concussive injury, but this finding should be further studied in a larger sample of athletes with recurrent in-season concussions.

Author Contributions: As principal investigator, Dr Guskiewicz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Guskiewicz, McCrea, Randolph, Kelly.
Acquisition of data: Guskiewicz, McCrea, Marshall, Onate.
Analysis and interpretation of data: Guskiewicz, Marshall, Cantu, Randolph, Barr, Kelly.
Drafting of the manuscript: Guskiewicz, McCrea, Marshall, Randolph, Barr, Kelly.
Critical revision of the manuscript for important intellectual content: Guskiewicz, McCrea, Marshall, Cantu, Randolph, Barr, Onate, Kelly.
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